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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Wilfred H. Nelson et al.	**GROUP:**	1641
SERIAL NO:	08/818,534	**EXAMINER:**	J. Hines
FILED:	March 14, 1997		

FOR: **DIRECT DETECTION OF BACTERIA-ANTIBODY COMPLEXES VIA UV RESONANCE RAMAN SPECTROSCOPY**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE

The Office Communication dated December 12, 2003 has been received and carefully considered.

The Examiner has objected to the appeal brief as presenting an improper grouping of the claims.

CERTIFICATE OF MAILING (37 CFR 1.8(a))

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date indicated below in an envelope as "First Class Mail" addressed to the: Commissioner of Patents, P.O. Box 1450 Alexandria, VA 22313-1450

Date: 01/06/04

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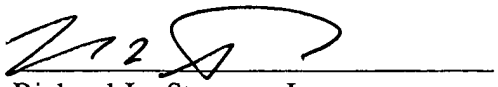
(Signature of person mailing paper)

The Appeal Brief has been amended to state that claims 9, 2, 10, 11 and 13 stand or fall together.

Respectfully submitted



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APPEAL BRIEF

Pursuant to 35 U.S.C. §134 and 37 C.F.R. §§1.191, 1.192 and 1.196, Applicants respectfully appeal to the Board of Patent Appeals and Interferences from the Examiner's final rejection of applicant's Patent Application Ser. No. 08/818,534 filed 03/14/1997.

1. Real Party in Interest

The real party in interest in the assignee, the Board of Governors for Higher Education, State of Rhode Island and Providence Plantations.

2. Related Appeal and Interferences

The present application has no pending related appeals or interferences.

3. STATUS OF CLAIMS

Claims 2, 9, 10, 11, 12, 13, 14, 15 and 16 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 12, 14, 15 and 16 have been deleted in a Rule 116 Amendment filed concurrently herewith.

Claims 12, 14, 15 and 16 stand rejected under 35 U.S.C. 102(b) as being unpatentable over Nelson et al. (U.S. Patent 4,487,198). Claims 12, 14, 15 and 16 have been deleted in a Rule 116 Amendment filed concurrently herewith.

Claims 2, 9, 10 12, 14, 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. in view of Tarcha et al. (U.S. Patent 5,266,498). Claims 12, 14, 15 and 16 have been deleted in a Rule 116 Amendment filed concurrently herewith.

Claim 13 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. and Tarcha et al., and further in view of Muller (U.S. Patent 5,126,244).

Claims 2, 9, and 10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. in view of Chadha et al. (Ultraviolet micro-Raman spectrograph for the detection of small numbers of bacterial cells).

4. STATUS OF AMENDMENTS

A Rule 116 Amendment is being filed concurrently herewith. The Amendment corrects the informalities in the drawing and deletes claims 12, 14, 15 and 16.

5. SUMMARY OF THE INVENTION

The invention includes a method for detecting the presence of a specific microorganism having a characteristic resonance enhanced Raman backscattered energy spectrum produced by irradiating nucleic acids in the microorganism at a wavelength between 242-257 nm in a sample. See specification on page 3, last paragraph, bridging to page 4, first paragraph. The sample is contacted with a medium comprising solid phase immobilized antibodies which specifically bind to a characteristic cell surface antigen on the microorganism to form an antigen-antibody complex. See specification on page 4, first paragraph, bridging to page 5, first and second paragraphs and page 6, first and third paragraphs, bridging to page 7, first paragraph. The solid phase is irradiated with a laser light of 242-257 nm to produce a resonance enhanced Raman backscattered energy. See specification on page 6, first and second paragraphs. The induced spectrum is then compared with the characteristic spectrum to detect the presence of the microorganism in the sample. See specification on page 4, paragraph 2. The method detects the presence of the

microorganism when at least a 200:1 ratio of solid phase immobilized antibodies in the medium to microorganism in the sample exists. See specification on page 3, last paragraph, to page 4, first paragraph, and page 5, third paragraph.

6. ISSUES

The issues before the Board in this appeal are whether the Examiner was correct in:

a) rejecting independent claim 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, claims 2, 10, 11 and 13 being dependent thereon;

b) rejecting independent claim 9 under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. in view of Tarcha et al., dependent claims 2, 10, 11 and 13 being rejected on the same or primarily the same premise as independent claim 9; and

c) rejecting independent claim 9 under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. in view of Chadha et al., dependent claims 2, and 10 being rejected on the same or primarily the same premise as independent claim 9.

7. GROUPING OF CLAIMS

For the purpose of this appeal, claims 9, 2, 10, 11 and 13 stand or fall together. Claims 12, 14, 15 and 16 have been deleted in the Rule 116 Amendment that is being filed concurrently herewith.

8. ARGUMENT

A. The Examiner was incorrect in rejecting claim 9 under 35 U.S.C. 112, second paragraph

Claim 9 recites in part:

"...the method detecting the presence of the microorganism when at least a 200:1 ratio of solid phase immobilized antibodies in the medium to microorganism in the sample exists."

To support the indefiniteness rejection of claim 9 the Examiner states:

"Because one could not know whether there was at least a 200:1 ratio of immobilized antibodies to microorganism, unless one knew how many microorganisms were present in the sample and one would not how many microorganisms were present in the sample before the method of detection was performed, thus the term is relative."

See enumerated paragraph 4 of the Final Office Action dated November 1, 2002. The above recited feature of claim 9 defines the sensitivity of the method. The knowledge of others with respect to how many microorganisms are present in the sample before the limitations of the method are performed is simply not relevant to the issue of whether the defined recited sensitivity of the method is clear to one of skill in the art. It is respectfully submitted that one of skill in the art, upon reading claim 9, would clearly understand that the above recited feature merely defines the sensitivity of the claimed method. In view of the foregoing, it is respectfully submitted that the Examiner's rejection should be withdrawn.

B. The Examiner was incorrect in rejecting claim 26 under 35 U.S.C. 103(a) as being unpatentable over Nelson et al. in view of Tarcha et al.

Claim 9, and claims 2, 10, 11 and 13 dependent thereon, are directed to a method for

detecting the presence of a specific microorganism having a characteristic resonance enhanced Raman backscattered energy spectrum produced by irradiating nucleic acids in the microorganism at a wavelength between 242-257 nm in a sample that comprises contacting the sample with a medium comprising solid phase immobilized antibodies which specifically bind to a characteristic cell surface antigen on the microorganism to form an antigen-antibody complex, irradiating the solid phase with a laser light of 242-257 nm to produce a resonance enhanced Raman backscattered energy and comparing the induced spectrum with said characteristic spectrum to detect the presence of the microorganism in the sample wherein the method detects the presence of the microorganism when at least a 200:1 ratio of solid phase immobilized antibodies in the medium to microorganism in the sample exists. It was unexpectedly discovered that a high ratio of antibodies in the medium to microorganism in the sample did not produce resonance Raman spectra that interfered with resonance Raman spectra of a microorganism when irradiated with light in the range of about 242-257nm. See specification on page 5, second and third paragraphs. This discovery was unexpected because antibodies, which comprise aromatic amino acids, were known in the art to emit resonance Raman spectra.

Nelson et al. discloses a method for identifying bacteria using resonance backscattered energy spectra. The method includes irradiating a sample of bacteria with a laser and identifying the bacteria based on the detected resonance Raman energy spectra of the irradiated bacteria. See col. 2, lines 10-24 and col. 5, lines 21-35.

Tarcha et al. discloses a ligand binding assay for an analyte using surface enhanced Raman scattering wherein a complex that includes the analyte, an antibody having an affinity for the analyte, a Raman-active reporter and a particle having a metallic surface is formed and irradiated. The resultant resonance Raman spectra of the Raman-active reporter, enhanced by the metallic

surface, is measured. See col. 5, lines 56-69, bridging to col. 6, lines 1-5 and col. 16, lines 1-20, in Tarcha et al. In contrast to Applicants' claimed method, the detection of the analyte in the sample is based on the measured resonance Raman spectra of the Raman-active reporter, not the analyte.

Chadha et al. discloses the immobilization of bacteria to a quartz plate coated with polylysine, the irradiation of the immobilized bacteria with light and the collecting the emitted resonance Raman energy spectra of the irradiated immobilized bacteria. See Chada et al. at page 3091 bridging to page 3092. The irradiate immobilized bacteria are detected based on the collected resonance Raman energy spectra. See Chada et al. at page 3092. Significantly, polylysine does not contain aromatic amino acids.

To support the obviousness rejection, the Examiner states:

"One would expect reasonable success by exchanging polylysine immobilization for site-specific immobilized antibodies when both techniques are specifically used to immobilize an analyte for Raman analysis and both techniques are known to be compatible with Raman analysis, when Tarcha et al, teach employing immobilized antibodies that would increase the sensitivity of the assay while such binding increases specificity in Raman analysis. Moreover, Tarcha et al., teach antibodies can be used with Raman analysis to provide microorganism specific analysis and antibody immobilization allows the percentage of capture sites available to be up to 75% or more of the number of capture molecules which increases the sensitivity of the assay."

See enumerated paragraph 8 of the Final Office Action dated November 1, 2002. The Declaration of Chris Brown that was filed on January 2, 2002 and received by the Patent Office on January 15, 2002 (hereinafter "the Brown Declaration") attests to the fact that at the time Applicants' invention was made it was know to those of skill in the art that aromatic amino acids produced resonance Raman spectra when irradiated with light having a wavelength in the range of about 242-257. See paragraph 6 of the Brown Declaration. This particular fact concerning the properties of aromatic amino acids is supported by the publications that were attached to the Brown Declaration as Exhibits A, B and C. The Brown Declaration further attests that because

antibodies are comprised of aromatic amino acids, one of skill in the art would have expected that the irradiation of antibodies and complexes comprised of an antibody coupled to the antigen of a microorganism with light having a wavelength in the range of about 242-257 would produce resonance Raman spectra that would interfere with the resonance Raman spectra of the coupled microorganisms when the method of claim 9 was practiced. See paragraph 7 of the Brown Declaration. However, contrary to the expectations referred to in paragraph 7 of the Brown Declaration, the antibodies and the antibodies of such complexes did not produce resonance Raman spectra which interfered with the resonance Raman spectra of the microorganism when the method of claim 9 was practiced. That is, when the method of claim 9 was practiced, it was unexpectedly discovered that resonance Raman spectra of the antibodies when irradiated with light as recited in claim 9 did not interfere with the resonance Raman spectra of the microorganisms when a high ratio of antibodies in the medium to microorganism in the sample existed. See specification on page 5, second paragraph.[1]

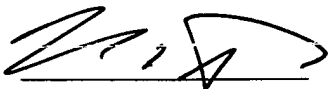
In view of the above, one of ordinary skill in the art would not have modified the method disclosed in Nelson et al. in view of Tarcha et al. and/or Chadha et al. to produce the method recited in claim 9 with a reasonable expectation of success because at the time Applicants' invention was made, one of ordinary skill would have expected that irradiating the antibodies of the recited complexes in accordance with claim 9 would result in the emission of resonance Raman spectra that would interfere with the resonance Raman spectra of the microorganisms thereby rendering the claimed method ineffective.

[1] In response to the Examiner's comments with respect to the probative value of the Brown Declaration set forth in the Office Action dated May 7, 2002, Applicants submit that it is clear from the Declaration that based on the knowledge of those of skill in art in regard to the properties exhibited by aromatic amino acids when irradiated with light within the claimed range set forth in claim 9, it would have been unexpected that the resonance Raman spectra of antibodies, which are comprised of aromatic amino acids, would not have interfered with the resonance Raman spectra of the immobilized microorganisms in the sample when at least a 200:1 ratio of solid phase immobilized antibodies in the medium to microorganism in the sample exist.

SUMMARY

For all of the foregoing reasons, applicant respectfully requests that the Board of Patent Appeals and Interferences reverse the Examiner's final rejection of claim 9 and claims 2, 10, 11 and 13 dependent thereon.

Respectfully submitted,



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9. APPENDIX

APPEALED CLAIMS

2. The method of claim 9 wherein the medium is a fluid medium and the microorganism is a bacterium.

9. A method for detecting the presence of a specific microorganism in a sample, the microorganism having a characteristic resonance enhanced Raman backscattered energy spectrum produced by irradiating nucleic acids in the microorganism at a wavelength between 242-257 nm, the method comprising:

(a) contacting the sample with a medium comprising solid phase immobilized antibodies which specifically bind to a characteristic cell surface antigen on the microorganism to form an antigen-antibody complex, thereby immobilizing the microorganism on the solid phase;

(b) irradiating the solid phase of step (a) with a laser light of 242-257 nm to produce a resonance enhanced Raman backscattered energy; and

(c) comparing the induced spectrum of step (b) with said characteristic spectrum to detect the presence of the microorganism in the sample, the method detecting the presence of the microorganism when at least a 200:1 ratio of solid phase immobilized antibodies in the medium to microorganism in the sample exists.

10. The method of claim 9 wherein the solid phase a step (a) is washed to remove unbound sample and medium before the irradiating step (b).

11. The method of claim 9 wherein the characteristic spectrum is at 1498 cm^{-1}.

13. The method of claim 2 wherein the bacterium is *E.coli* and the antibodies are anti-*E.coli*.